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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,045	10/20/2003	Thomas B. Ottoboni	375430-002t1d1c1	3501

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	**PAPER NUMBER**
1617	
MAIL DATE	**DELIVERY MODE**
08/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,045	OTTOBONI ET AL.	
	Examiner	Art Unit	
	Umamaheswari Ramachandran	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 6/13/2007
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 6/4/2007 amending claims 1, 10, 11 and 12 and adding new claims 15 and 16. Claim 9 is canceled. Claims 1-8, 10-16 are pending.

Response to Remarks

The rejection of claims 1-14 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16, 19, 20, and 25-41 of U.S. Patent No. US 6,193,951 is withdrawn due to the filing of Terminal Disclaimer by the Applicants'. The rejection of claims 1-14 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3, 16-24, and 28-37 of copending Application No. 09/637,516 in view of Bichon et al. (EP 0 458 745) is withdrawn due to the filing of Terminal Disclaimer by the Applicants'. The rejection of claims 1-14 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of copending Application No. 10/977,100 is maintained and is given below for Applicants' convenience. Applicant's arguments filed 11/20/2006 regarding 35 U.S.C 103 rejection of claims 1-14 under 35 U.S.C. 103(a) as being unpatentable over Bichon et al. (EP 0 458 745) (Also see the corresponding US Patent 5,840,275) in view of Hilmann et al. (US 4,466,442), and further in view of Berstein et al. (WO 91/06287) have been fully considered but they are not persuasive. The amendments and addition of new claims necessitated a modified rejection and are given below for Applicants' convenience. The Office Action is made Final.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of copending Application No. 10/977,100. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '100 are within the scope of the instant claims and thus anticipate the instantly claimed invention. Specifically, '100 teach compositions comprising microparticles and the herein-claimed excipients (glycine, polyethylene glycol 3350, poloxomer, etc.). '100 teaches that the microparticles are comprised of two layers, said layers being comprised of the herein-claimed biodegradable polymers (polylactide) and glutaraldehyde cross-linked albumin. '100 teach that the microparticles have a hollow core filled with nitrogen. The amounts of the components are more explicitly defined in '100 and the scope is thus narrower than for the instantly claimed compositions. Therefore, '100 anticipate the instantly claimed compositions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bichon et al. (Applicant-cited reference on IDS: EP 0 458 745) (Also see the corresponding US Patent 5,840,275) in view of Hilmann et al. (US 4,466,442), and further in view of Berstein et al. (Applicant-cited reference on IDS: WO 91/06287).

Bichon et al. teach compositions comprising microparticles filled with air or gas for use in ultrasonic echography (col. 1, lines 1-15; claims 1-3). Bichon et al. teach that the microparticle compositions can be prepared in aqueous solutions or in the solid form (i.e., the isolated cake or powder) for use in echography (col. 1, lines 1-8). Bichon et al. teach that the art recognizes that microparticles used for echography should have

diameters in the range of about 0.5 to 10 micrometers (col. 2, lines 26-46). Bichon et al. exemplify a range of polymers useful for forming the membrane coat of the microparticles, including biodegradable polymers such as polylactides, and proteins such as albumin (col. 9, line 2-col. 10, line 8; claim 6). Bichon et al. teach that cross-linking proteins, such as albumin, with glutaraldehyde is an art-recognized method of forming microparticle membrane shells (col. 3, lines 20-53). Bichon et al. teach that the inclusion of sugars, such as sucrose, in order to stabilize the microparticles is known (col. 2, lines 8-46; col. 8, lines 20-30; col. 10, line 54-col. 11, line 4). Bichon et al. teach the inclusion of surfactants to increase membrane elasticity (claim 11; col. 2, lines 31-46; col. 10, lines 34-46). Bichon et al. also teach the inclusion of "polyethylene glycol of moderate to low M_W" (e.g. PEG 2000)) as membrane-plasticizing agents (col. 10, lines 44-46).

Bichon et al. do not explicitly teach the use of nitrogen as the gas within the core. Bichon et al. do not teach a microparticle with a membrane comprised of two layers of the polymers.

Hilmann et al. teach that nitrogen is a preferred gas for incorporation into microparticles for use in echography (claim 14).

Berstein et al. teach the layering of polymers to form microparticles of various size, durability, and release properties. Berstein et al. teach that the microspheres can have layers containing different properties (p. 7, first full paragraph). Berstein et al. teach that the same polymers exemplified by Bichon et al. can be layered to form multilayer microparticles (pp. 13-15). Berstein et al. teach the charge on the proteins

can also be modified by crosslinking amino acids to the protein using glutaraldehyde (p 13, lines 9-12). Berstein et al. teach that amino acids are one type of agent than can be included in the microparticles (p. 5, last paragraph). Bernstein teach that protein microspheres can be used in a method other than drug delivery such as to release enzymes, pesticides, fertilizers etc, provide biodegradable non toxic diagnostic agents for use in methods such as radioimaging (p 3, lines 12-14, 19-21).

It would have been obvious to the person of ordinary skill in the art at the time of invention to produce a multilayer microparticle comprising the polymers of Bichon et al., to fill the core of the microparticles with nitrogen.

The person of ordinary skill in the art would have been motivated to layer the polymers of Bichon et al. because Berstein et al. teach that by layering the polymers, the size, durability, and release properties of microspheres can be modulated. The person of ordinary skill in the art would have expected success because Berstein et al. teach that the same polymers exemplified by Bichon et al. can be layered in the preparation of the microparticles.

The person of ordinary skill in the art would have been motivated to use nitrogen as the gas in the core of the particles with a reasonable expectation of success because Bichon et al. and Berstein et al. teach that the microparticles can be used in echography when a gas is incorporated into the microparticles, and Hilmann et al. teach that nitrogen is a preferred gas for inclusion in microparticles used for echography.

Response to Arguments

Applicants' argue that Bernstein et al. teach only hydrophobic proteins and the patent office has no basis to conclude that other proteins, and in particular the proteins mentioned in the Bichon et al reference could be used in the polymer-protein composite microspheres. In response, Bernstein, teach the concept of layering of polymers to form microparticles. The reference teach that microspheres can be a polymer core within the protein microsphere (p 5, lines 1-19) and defines "composite microsphere" is a microsphere formed of at least two different materials, either a protein and a polymer or two protein and teaches in general a method of preparation of protein microspheres. Thus Bernstein teaches the concept of protein microspheres with polymer and it would have been obvious to one of ordinary skill in the art to use the concept of composite microspheres with other proteins such as serum albumin. The person of ordinary skill in the art would have expected success because Berstein et al. teach that the same polymers exemplified by Bichon et al. can be layered in the preparation of the microparticles. Bernstein teaches (p 8, lines 14-21) "The process described herein yields protein microspheres having a diameter of between nanometers and micrometers, with an average diameter between 0.01 micron to less than about 100 microns, having incorporated therein a compound to be delivered or released at a desired time and or/site. In the preferred method, the microspheres are stored frozen to enhance the stability of incorporated compounds over extended periods of time". Hence a person of ordinary skill in the art would have been motivated to use the process taught

by Bernstein in making composite microspheres because of the stability, size variability and release properties of the protein microspheres.

Applicants' argue Bernstein et al. does not teach the concept that 'by layering the polymers, the size, durability, and release properties of microspheres can be modulated" (Applicants' arguments p 6, lines 33-36). In response, Bernstein teaches "Both the release of the incorporated compound and the bioerosion of the matrix are releated to the molecular weight of PLA, PGA or PLA/PGA. The higher molecular weights, weight average molecular weights of 90,000 or higher, result in polymer matrices which retain their structural integrity for longer periods of time; while lower molecular weights, weight average molecular weights of 30,000 or less, result in both slower release and shorter matrix lives" (p 14, lines 19-26). The reference further teaches that matrices are made of either a protein mixture or a protein-polymer mixture (p 14, para 4, lines 1-2) and the reference teach a polymer core within the protein microsphere (p 5, line16). Bernstein teaches that the composite matrices can take one of several forms; protein microspheres with a polymer coating; polymer microparticles or microcapsules encapsulated by protein etc (p 15, lines 2-9). Hence the reference teaches the layering of polymers and the modulation of the size, durability, and release properties of microspheres.

Applicants' argue that for a rejection under U.S.C 103(a) based upon combination of references to be proper, the references must teach each and every element in the claim. In response, Bichon et al. teach compositions comprising microparticles filled with air or gas and air contains 79% nitrogen. Bichon et al. teach

that the art recognizes that microparticles used for echography should have diameters in the range of about 0.5 to 10 micrometers. Bichon et al. exemplify a range of polymers useful for forming the membrane coat of the microparticles, including biodegradable polymers such as polylactides, and proteins such as albumin. Bichon et al. teach that cross-linking proteins, such as albumin, with glutaraldehyde is an art-recognized method of forming microparticle membrane shells. Bichon et al. teach that the inclusion of sugars, such as sucrose, in order to stabilize the microparticles is known. Bernstein teach that microspheres can be made as a polymer core within the protein microsphere and Hilmann et al's teachings clearly indicate that nitrogen, a physiologically acceptable gas can be incorporated into microparticles. One of ordinary skill in the art would have been motivated to derive a composition comprising microparticles comprising a shell enclosing a gas filled hollow core, comprising an outer layer composes of cross-linked amphilic protein and an inner layer composed of biodegradable synthetic polymer because of expectation of success as Bichon teach that cross-linking proteins, such as albumin, with glutaraldehyde is an art-recognized method of forming microparticle membrane shells and further teach the microparticles are filled with air or gas and the size of the microparticles in the range of about 0.5 to 10 micrometers. Bernstein teach that microspheres can be made as a polymer core within the protein microsphere and Hilmann et al's teachings clearly indicate that nitrogen, a physiologically acceptable gas can be incorporated into microparticles. Bichon and Bernstein teach the biodegradable polymers as claimed in the instant application. All the elements of the instant claims are taught by the references Bichon, Bernstein and Hilmann.

Conclusion

No Claims are allowed.

Applicant's amendment and the addition of new claims necessitated the modified rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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SUPERVISORY PATENT EXAMINER